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31/19, 31/215

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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,  
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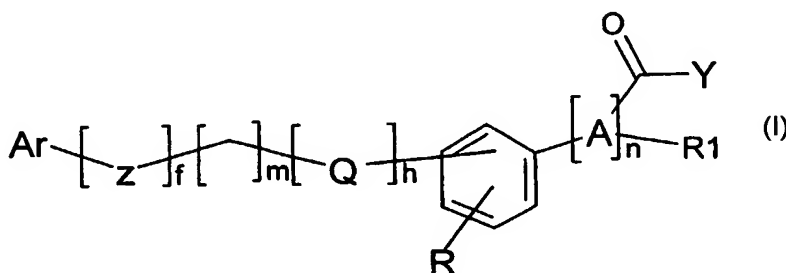
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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: PHENY(ALKYL)CARBOXYLIC ACID DERIVATIVES AND DIONIC PHENYLALKYLHETEROCYCLIC  
DERIVATIVES AND THEIR USE AS MEDICINES WITH SERUM GLUCOSE AND/OR SERUM LIPID LOWERING  
ACTIVITY



(57) Abstract: Formula (I) compounds are described: Where the groups are as defined here below, and their use as medicines, particularly as serum glucose and serum lipid lowering agents. Said medicines are useful for the prophylaxis and treatment of diabetes, particularly type 2, and its complications, Syndrome X, the various forms of insulin resistance, and hyperlipidaemias, and present reduced side effects, and, particularly, reduced or no liver toxicity.

## INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>					
IPC 7	C07D209/08	C07D209/12	C07D213/30	C07D213/20	C07D277/20
	C07D277/34	C07C69/734	C07C271/58	C07C271/48	C07C233/66
	C07C235/60	C07C217/76	A61K31/427	A61K31/19	A61K31/215
According to International Patent Classification (IPC) or to both national classification and IPC					
<b>B. FIELDS SEARCHED</b>					
Minimum documentation searched (classification system followed by classification symbols)					
IPC 7 C07D A61K A61P					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
WPI Data, EPO-Internal, CHEM ABS Data, INSPEC					
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KITAJIMA, HIROSHI ET AL: "Preparation of 3-Aromatic-substituted propionic acid or acrylic acid derivatives as antidiabetics" retrieved from STN Database accession no. 134:41915 XP002262201 abstract and RNs 312689-52-4, 312690-33-8, 312690-69-0, 312690-71-4, 312690-73-6, 312689-53-5, 312690-29-2 & JP 2000 344748 A (WELLFIDE K. K., JAPAN) 12 December 2000 (2000-12-12)				1,8,9
X	WO 99 62871 A (ASTRA AB) 9 December 1999 (1999-12-09) examples 26b, 98-100; claims 1,38 --- -/-				1,8,9
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.					
<input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family					
Date of the actual completion of the international search			Date of mailing of the international search report		
20 November 2003			03/12/2003		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer  Alfaro Faus, I		

## INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHINKAI H ET AL: "ISOXAZOLIDINE-3,5-DIONE AND NONCYCLIC 1,3-DICARBONYL COMPOUNDS AS HYPOGLEMIC AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 41, no. 11, 1998, pages 1927-1933, XP002151949 ISSN: 0022-2623 table 1, compound 18 ----	1,8,9
X	EP 0 930 299 A (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21) claims 1,4,7; examples 57,58 ----	1,8,9
X	US 5 306 726 A (HULIN BERNARD) 26 April 1994 (1994-04-26) column 1 (16-21) and column 27 (65-66) ----- -/-	1,8,9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- \*G\* document member of the same patent family

Date of the actual completion of the international search

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Authorized officer

Alfaro Faus, I

## INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 232 945 A (HULIN BERNARD) 3 August 1993 (1993-08-03) column 1 (9-22); column 24 (37-38) ---	1,8,9
X	WO 91 19702 A (PFIZER) 26 December 1991 (1991-12-26) page 54, lines 3-8, claims 1, 34 ---	1,8,9
X	EP 0 008 203 A (TAKEDA CHEMICAL INDUSTRIES LTD) 20 February 1980 (1980-02-20) claims 1 and 7; examples 1212,13,16-24, 38-42, 13 ---	1,8,9
X	EP 0 193 256 A (TAKEDA CHEMICAL INDUSTRIES LTD) 3 September 1986 (1986-09-03) claim 6 ---	1,8,9
X	MOMOSE Y ET AL: "STUDIES ON ANTIDIABETIC AGENTS. X. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PIOGLITAZONE AND RELATED COMPOUNDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 39, no. 6, June 1991 (1991-06), pages 1440-1445, XP000986045 ISSN: 0009-2363 table II and Table III (Y=0) table II ---	1,8,9
X	EP 0 528 734 A (ADIR) 24 February 1993 (1993-02-24) examples 7,8,21,22,38 ---	1,8,9
X	EP 0 676 398 A (SANKYO CO) 11 October 1995 (1995-10-11) claims 1,27; examples 3,4,6 ---	1,8,9
X	EP 0 846 693 A (KYORIN SEIYAKU KK) 10 June 1998 (1998-06-10) examples 15-26,28,37,38; claims 1,14 claim 1; tables 1,14 ---	1,8,9
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## INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  KINOSHITA, SUSUMU ET AL: "Preparation of  N-benzyl(dioxothiazolidyl)benzamides and  their use as oral antidiabetics and  hypolipemic agents"  retrieved from STN  Database accession no. 128:13261  XP002262202  abstract and RNs 199167-85-6, -86-7,  -87-8, -89-0, -81-2, -82-3, -83-4, -84-5  &amp; JP 09 301963 A (KYORIN PHARMACEUTICAL  CO., LTD., JAPAN)  25 November 1997 (1997-11-25)</p>	1,8,9
X	<p>EP 0 881 219 A (KYORIN SEIYAKU KK)  2 December 1998 (1998-12-02)  claims 1,8; example 25</p>	1,8,9
X	<p>SOHDA T ET AL: "STUDIES ON ANTIDIABETIC  AGENTS. III. 5-ARYLTHIAZOLIDINE-2,4-DIONES  AS POTENT ALDOSE REDUCTASE INHIBITORS"  CHEMICAL AND PHARMACEUTICAL BULLETIN,  PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO,  JP,  vol. 30, no. 10, 1982, pages 3601-3616,  XP002024094  ISSN: 0009-2363  table III, compounds 32-35</p>	1,8,9
X	<p>EP 0 526 658 A (KYORIN SEIYAKU KK)  10 February 1993 (1993-02-10)  claims 1,6; example 60</p>	1,8,9
X	<p>CURTIS, NEIL R. ET AL: "Synthesis and SAR  of diiodotyrosine-derived glycine-site  N-methyl-D-aspartate receptor ligands"  BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS  (1996), 6(10), 1145-1150 ,  XP004134886  compound 18</p>	1,8
X	<p>WO 01 40170 A (ASTRAZENECA AB )  7 June 2001 (2001-06-07)  examples 11(a), 15(a), 21(a), 21(b)</p>	1
X	<p>WO 00 78312 A (MERCK)  28 December 2000 (2000-12-28)  preparative examples 4, 61, 67</p>	1

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## INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KITAJIMA, HIROSHI ET AL: "Hybridization of non-sulfonylurea insulin secretagogue and thiazolidinedione-derived insulin sensitizer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2000), 10(21), 2453-2456 , XP004224238 compound 12 (R=5-ethyl-2-pyridyl) -----	1
X	WO 94 19335 A (OTSUKA) 1 September 1994 (1994-09-01) page 90, line 10 -----	1

# INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-4, 6-9 ( in part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 6-9 ( in part)

Present claims 1-4 and 6-9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, as disclosed in claim 5, where Ar is phenyl, naphthyl, 1-indolyl, 3-indolyl, 2 pyridyl, or pyridinium, all of them optionally substituted as indicated in claim 1 and 3; -'z!f'CH2!m'Q!h is -CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-, -NH(C=O)O-, -CH<sub>2</sub>NH(C=O)O-, or -CH<sub>2</sub>NH(C=O)-; the phenylene moiety is a p-phenylene, a m-phenylene or a 2-CH<sub>3</sub>O-m-phenylene group, and the -'A!nR1C(=O)-Y group represents a thiazolidine-2,4-dione or a carboxylic acid or ester as defined in claim 1

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



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PCT/IT 03/00007

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